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Original Article

Epidemiology of *Escherichia coli* as a Critical Pathogen of Bloodstream Infection Patients in Dr. Soetomo General Hospital, Surabaya, Indonesia

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ABSTRACT

Bloodstream infections (BSI), caused primarily by multidrug-resistant Escherichia coli, are a significant cause of morbidity and mortality worldwide. This study aims to evaluate the epidemiology of E. coli as a critical pathogen in patients with bloodstream infections in a tertiary referral hospital. This is a retrospective study using a descriptive observational research design. This study used a medical record instrument for bloodstream patients in Dr. Soetomo Hospital's inpatient ward with Gram-negative bacteria results of blood cultures in the Clinical Microbiology Laboratory from April 2021 to September 2021. The observed variables include; antimicrobial sensitivity, patient clinical characteristics, demographic data, clinical diagnosis, and clinical outcome. In 6 months, 276 Gram-negative bloodstream infection patients were treated at Dr. Soetomo Hospital. The proportion of E. coli was 17 %. The main characteristics of patients were over 60 years old (28%), and 54% were female. 63% of E. coli were ESBL, and 9% were carbapenem-resistant microorganisms. High antimicrobial resistance was found in quinolones (100%), ampicillin (93%), piperacillin (74%), tetracycline (72%), ceftriaxone (66%), cefotaxime (65%), ceftazidime (60%), cefazolin (65%), and trimethoprim-sulfamethoxazole (65%). The most common potential determinant profile discovered was linked to immunocompromised status due to malignancy. The high number of antimicrobial-resistant bacteria showed the importance of strict infection control and updated epidemiology data as a guide for empirical antimicrobial therapy.

Keywords: *bloodstream infection; E.coli; epidemiology; ESBL; resistance*

ABSTRAK

Infeksi aliran darah (IAD), yang terutama disebabkan oleh Escherichia coli yang bersifat multi-drug resistance microorganisms (MDRO), merupakan penyebab signifikan morbiditas dan mortalitas di seluruh dunia. Penelitian ini bertujuan untuk mengevaluasi epidemiologi E. coli sebagai patogen pada pasien infeksi aliran darah di rumah sakit rujukan tersier. Penelitian ini merupakan penelitian deskriptif dengan desain penelitian observasional menggunakan alat rekam medis aliran darah pasien di ruang rawat inap RSUD Dr. Soetomo dengan bakteri Gram negatif hasil kultur darah di Laboratorium Mikrobiologi Klinik pada bulan April 2021 sampai September 2021. Variabel yang diamati meliputi; sensitivitas antimikroba, karakteristik klinis pasien, data demografis, diagnosis klinis, dan hasil klinis. Dalam 6 bulan, didapatkan 276 pasien infeksi aliran darah Gram-negatif dirawat di RS Dr. Soetomo. Proporsi E. coli adalah 17%. Karakteristik utama pasien berusia di atas 60 tahun (28%), dan 54% berjenis kelamin perempuan. 63% E. coli adalah ESBL, dan 9% adalah mikroorganisme yang resisten terhadap karbapenem. Resistensi antimikroba yang tinggi ditemukan pada kuinolon (100%), ampisilin (93%), piperacillin (74%), tetrasiklin

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(72%), ceftriaxone (66%), cefotaxime (65%), ceftazidime (60%), cefazolin (65%), dan trimethoprim-sulfamethoxazole (65%). Profil penentu potensial yang paling umum ditemukan terkait dengan status immunocompromised karena keganasan. Tingginya jumlah bakteri resisten antimikroba menunjukkan pentingnya pengendalian infeksi yang ketat dan data epidemiologi terkini sebagai panduan terapi antimikroba empiris.

Kata kunci: *E. coli; epidemiologi; ESBL; infeksi aliran darah; resistensi*

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INTRODUCTION

Bloodstream infection (BSI) is a big challenge of infectious diseases. It represents 40% of community-acquired (CA) cases, hospital-acquired (HA) sepsis and septic shock, and approximately 20% of ICU-acquired cases.[1] It is invariably associated with poor outcomes significantly when adequate antimicrobial therapy and source control are delayed.[2] The pathogens causing bloodstream infection majority caused by Gram-negative bacteria, including *E. coli*.[3, 4] *E. coli* is a bacteria that often has resistant mechanisms to multiple antibiotics. These bacteria have built-in resistance mechanisms and can pass on genetic material that allows other bacteria to become drug-resistant. Because of this, *E. coli* was covered as a critical pathogen by the WHO in 2017.[5,6] BSI caused by multi-drug resistant (MDR) organism make the management difficult because the antibiotic therapy is limited and unsuitable empirical antibiotic treatment is given. BSI by MDR *E. coli* was associated with poorer outcomes and a higher overall mortality rate.[7]

E. coli, including Extended-spectrum beta-lactamase (ESBL) producing and Carbapenem-resistant, can cause severe and frequently lethal infections, especially bloodstream infections (BSIs).[4,8,9] ESBLs-producing bacteria can hydrolyze broad-spectrum cephalosporins, monobactams, and penicillins, while Carbapenem-resistant is an *E. coli* isolate resistant to ertapenem, imipenem, meropenem, or any carbapenem antimicrobial.[10] Bloodstream infection caused by those organisms represents a challenge due to the limitation of antimicrobials as a drug of choice; furthermore, it can cause significant morbidity and mortality.

The critical pathogens in bloodstream infection are majority caused by Gram-negative bacteria, the most frequent pathogen was *E. coli*[3,4] which could be characteristically different profiles in various hospitals or patient care units. In a hospital setting, it is crucial to evaluate and monitor the updated epidemiology of causative agents of infection due to the prevention and infection control program and the updated empirical antibiotics in the hospital. Therefore, epidemiological studies on microorganism infection must be updated periodically. This research focuses on local epidemiology data of *E. coli* as a pathogen detected in bloodstream infection, including the resistance pattern and the determinants factor related to invasive devices and immunocompromised conditions.

MATERIALS AND METHODS

Materials

We used data from the records of blood culture results from the Clinical Microbiology Unit and medical records of patients with Gram-negative bloodstream infection in inpatient wards of Dr. Soetomo Hospital from April 2021 until September 2021. Ethical clearance from the ethics committee has been obtained by number 0660/LOE/301.4.2/ X/2021.

Methods

This research is descriptive research. All medical records containing *Escherichia coli*

detected, antimicrobial sensitivity, and other determinant factors, i.e., patient clinical characteristics, demographic data, clinical diagnosis, history of invasive devices, antibiotic use, and clinical outcomes. In addition, species identification, antimicrobial susceptibility testing, and determination of resistant patterns, including ESBL-producing strains and Carbapenem-resistant strains, using BD BACTEC™ blood culture system and BD Phoenix™ system. Antimicrobial sensitivity interpreted based on Clinical Laboratory and Standards Institute (CLSI) guideline 2021. Statistical Analysis Data were analyzed with Microsoft Excel and presented in a frequency table with the percentage of each variable which was then converted into a descriptive form.

RESULTS AND DISCUSSION

There were 276 Gram-negative bacteria of a total of 973 (28.4%) positive blood cultures of hospitalized patients in Dr. Soetomo Hospital Surabaya within 6 months. *E. coli* was found in 48 patients of 276 Gram-negative bacteria (17%). It can be seen that *E. coli* was the third rank of Gram-negative bacteria causing bloodstream infection (Table 1). Forty-three of the 48 patients with *E. coli* bloodstream infection with the complete medical record were analyzed.

Table 1. Distribution of Gram-Negative Bacteria Detected of Bloodstream Infection in Dr. Soetomo Hospital, Surabaya, from April 2021 – September 2021

Gram-Negative Bacteria	n (%)
Acinetobacter baumannii/calcoaceticus complex	67 (24)
Klebsiella pneumoniae	63 (23)
Escherichia coli	48 (17)
Pseudomonas aeruginosa	22 (8)
Enterobacter cloacae	19 (7)
Other Gram-negative bacteria	57 (21)
Total	**276 (100)**

This study's results align with the surveillance study about the trend of bloodstream infection in the USA reported that the most prevalent Gram-negative bacteria causing bacteremia from 2005 until 2016 was *E. coli*, with an incidence range of 20-24%.[3] In comparison, *E. coli* also was found to be the most prevalent pathogen (32.8% of cases), followed by *Staphylococcus aureus* (20.6%), *Klebsiella pneumoniae* (16.1%), and *Pseudomonas aeruginosa* (11.6%), in a study of bloodstream infections at a major teaching hospital in Rome within 9 years period, according to Angelis et al.[4]

Another data of 382 BSI cases in a tertiary teaching hospital ICU revealed the most frequently isolated microorganisms to be *Klebsiella pneumoniae* (11.52%), followed by *Escherichia coli* (9.95%).[11] Furthermore study about the profile of blood culture of sepsis patients in the Intensive Care Unit (ICU) – Dr. Soetomo Hospital Surabaya revealed that Gram-negative bacteria were 25% of the total positive culture. Of the Gram-negative bacteria, Enterobacteriaceae showed a proportion of 59%, followed by *Acinetobacter baumannii* at 29%.[12]

The 43 *E. coli* strains isolated from the blood culture of BSI comprised 20 male patients and 23 females. This data aligns with a systematic literature review report that women were more likely than men to develop *E. coli* bacteremia overall. According to age group stratification, this connection was only present in young and middle-aged individuals; in adults over 60, the incidence rates for men and women were comparable.[13]

The age of the patients showed in Table 2, where the subjects were between 0.01 years (neonates) to 81 years, with the most age distribution being over 60 years, namely 12 patients. This data is in accordance with a systematic literature review report that the incidence rate considerably rose with age. With estimated rates of 110, 154, and 319 episodes per 100,000 person-years among those aged 60 to 69, 70 to 79, and 80 years and older, respectively, older individuals' incidence rates were higher than the population norm.[13]

Table 2. Age Distribution of Patients with Bloodstream Infection Caused by *E. coli*

Age Group (year)	n (%)
0–10	6 (14)
11–20	5 (12)
21–30	1 (2)
31–40	3 (7)
41–50	7 (16)
51–60	9 (21)
>60	12 (28)

Out of 43 patients, 16 (37%) were referred from other hospitals (Table. 3); this could be associated with the role of Dr. Soetomo hospital as the tertiary referral hospital. The primary diagnoses of patients in this study were grouped into several criteria, namely malignancy, coronavirus infection, primary infection other than BSIs, bile duct atresia, and other diagnoses composed of the small proportion of diagnoses listed in the footnotes of the table. The primary disease diagnosis was malignancy in 12 patients (28%), coronavirus infection in 11 patients (26%), primary infection other than BSIs in 8 patients (19%), bile duct atresia in 3 patients (7%), and others in 9 patients (21%). The most significant proportion of patients with primary diagnoses were malignancy and coronavirus infections.

Table 3. Characteristics of the Patients in the Study

Characteristics (n=43)	Patients (n/%)
Age (year; means, min-max)	43; 0.01–81
Gender (M/F)	20 (46)/23 (54)
Referral patients	16 (37)
Diagnosis for hospitalization	
Malignancy*	12 (28)
Coronavirus infection	11 (26)
Infection **	8 (19)
Bile duct atresia	3 (7)
Other ***	9 (21)
Nasogastric tube	27 (63)
Ventilator/Intubation	19 (44)
Surgery	14 (33)
Using a central venous catheter (CVC)	14 (33)
Immunosuppressant therapy in 30 days	13 (30)
Total of patients	43 (100)

*acute myeloid leukemia, acute lymphocytic leukemia, anaplastic anemia, Non-Hodgkin's lymphoma, malignant neoplasm of the placenta, malignant neoplasm of the ovary, malignant neoplasm of the cervix, malignant neoplasm of uteri, malignant neoplasm of the bile duct, malignant neoplasm of the pancreas

**septicemia, abscess of the liver, acute pancreatitis, pneumonia, cholecystitis, acute peritonitis, intestines tuberculosis, congenital pneumonia

***myelodysplastic syndrome, myasthenia gravis, morbidly adherent placenta, other and unspecified ovarian cysts, congenital hydronephrosis, acute renal failure, communicating hydrocephalus, burn multi regions

Several determinants were recorded, including invasive devices and others that may be associated with bacteremia (Table 3). The data showed the use of invasive devices was nasogastric tubes (63%), ventilators/ intubation (44%), and the central venous catheter (CVC) (33%). Furthermore, we found surgery cases (33%), immunosuppressant therapy (30%), and neutropenia (16%). A systematic literature review concluded that central and peripheral venous catheters increased the risk of *E. coli* bacteremia: by 10-fold and 7.5-fold, respectively. In contrast, suprapubic and urethral urinary catheters increased the risk by 6-fold and 3-fold, respectively.[13]

The proportion of patients with malignancy was relatively high, namely 12 patients (12%), consisting of 6 patients with leukemia and 6 with solid organ malignancy. This result supports the available epidemiological data that the percentage of bacteremia patients infected by *E. coli* is associated with particular underlying clinical conditions. A study by Bonten et al. mentioned that the highest rate of patients with bacteremia resulting from *E. coli* was lymphocytic leukemia and multiple myeloma (12–13%). The neoplastic disease has a relative risk (RR) of developing *E. coli* bacteremia 14.9 fold compared with the general population.[13]

The proportion of bacteremia cases with a primary diagnosis of COVID-19 was relatively high, namely 11 patients (26%). Bhatt et al[14] report that the bloodstream infections observed in patients with COVID-19 may have contributed to the more severe presentation and clinical course. Furthermore, it reflects other underlying physiological and immunological complications of COVID-19. Alternatively, a complicated hospital course may have contributed to more risk factors for developing bloodstream infections.[14] In this

research, 26% of COVID patients with co-infection by bloodstream infection due to *E. coli* need attention to the importance of surveillance and prevention of the possibility of a healthcare-associated infection BSIs.

No review of the source of the bloodstream infection was carried out in this study. However, several studies have reported that central line is the most common presumed source of bloodstream infections.[14]

Antimicrobial Resistance Profile

The microorganism was classified based on antimicrobial resistance profiles. Of 43 isolates, 15 (35%) were non-MDRO, 28 (63%) were ESBL-producing microorganisms, 4 (9%) were Carbapenem-resistant. In addition, three ESBL-producing microorganisms were Carbapenem-resistant microorganisms (Table 4).

Table 4. Types of Organisms Based on Antimicrobial Resistance Profile

Types of the Organism	n (%)
Non-MDRO	15 (35)
ESBL-producing strain	24 (56)
Carbapenem-resistant strain	1(2)
ESBL-producing strain AND Carbapenem-resistant strain	3 (7)
Total	43 (100)

The ESBL-producing bacteria were higher than the non-MDRO bacteria, 63% and 35%, respectively. This number was very high. The study showed that the prevalence of ESBL-producing bacteria is increased in the latest period. The clinical relevance of infections caused by ESBL-producing organisms has been outlined in several studies.[15,16] In a retrospective analysis of patients with *E. coli* BSI over four years in a teaching hospital, 58.9% developed ESBL-producing *E. coli*.[17]

No risk factor analysis for ESBL infection in this study, but several studies report that ESBL-producing *E. coli* bacteremia is associated with prior urinary tract infections,[17] previous cephalosporin exposure[17], central venous cathether[15], and history of admission to a long-term care hospital.[18]

Bloodstream infections, particularly BSIs due to MDR *E. coli*, can be caused by hospital-acquired or community-acquired infections. It has been widely reported that infections caused by MDR bacteria are associated with hospital/healthcare-associated infections. Several studies supported community-acquired BSIs by MDR bacteria, which reported the presence of carriers of ESBL-producing *E. coli* bacteria in communities with varying prevalence between different populations. [19,20,21]

Globally, an 8-fold growth in the bowel carriage rate of ESBL *E. coli* in the community during the last decade. The pooled incidence confirmed an upward trend of *E. coli* carriage in the community, growing from 2.6% in 2003–2005 to 21.1% in 2015–2018. Over the entire period, the highest carriage rate happened in South-East Asia (27%), while the lowest happened in Europe (6.0%).[22] In addition, the carrier of ESBL-producing *E. coli* bacteria was reported to develop bloodstream infection.[19]

BSI caused by emerging multidrug-resistant *E. coli* strains is more challenging to treat and confers a higher risk of death. Although it cannot be concluded that the cause of death was purely due to *E. coli* BSI, 68% of patients died in this study. A study reported that in *E. coli* BSI, 50% of the patients died, and the mortality analysis showed that 33.3% of the deaths were associated with BSI.[23]

Table 5. Antibiotics Resistant Pattern of *E. coli* Isolated from Bacteremia Hospitalized Patients

Antibiotics	Tested number	Resistance n (%)
Ciprofloxacin	27	27 (100)
Levofloxacin	27	27 (100)
Ampicillin	42	39 (93)
Piperacillin	43	32 (74)
Tetracyclin	43	31 (72)
Cefotaxime	41	27 (66)
Cefazolin	43	28 (65)
Ceftriaxone	43	28 (65)
Trimetoprim-sulfametoxazole	43	28 (65)
Aztreonam	43	27 (63)
Ceftazidime	43	26 (60)
Moxifloxacin	42	25 (58)
Cefepime	37	17 (46)
Gentamicin	42	15 (36)
Ampicillin Sulbactam	43	10 (23)
Chloramphenicol	43	8 (19)
Amoxicillin-Clavulanate	42	7 (17)
Cefoxitin	37	5 (14)
Fosfomycin	42	5 (12)
Imipenem	41	4 (10)
Meropenem	42	4 (10)
Tigecycline	30	2 (7)
Cefoperazone-Sulbactam	43	2 (5)
Amikacin	43	1 (2)
Piperacillin Tazobactam	40	0 (0)

The antimicrobial resistance pattern of tested antimicrobials against *E. coli* from bloodstream infection patients in Table 5 revealed a high proportion of strains of *E. coli* were resistant to Ampicillin (93%), Piperacillin (74%), and tetracycline (72%). The resistance of third-generation cephalosporin ceftriaxone, cefotaxime, and ceftazidime was 66%, 65%, and 60%, respectively, while the fourth-generation cephalosporin cefepime was lower (46%). The resistance to trimethoprim-sulfamethoxazole was 65%. Carbapenem as a drug of choice for multi-drug resistance E coli showed resistance was 10%. A low proportion of strains of *E. coli* were resistant to tigecycline (7%), cefoperazone-sulbactam (5%), and amikacin (2%). No resistance to piperacillin tazobactam was found. Quinolone antibiotics (levofloxacin and ciprofloxacin) were tested only in 27 isolated, and the result was 100% resistance.

The resistance to several drugs, including carbapenem antibiotics (imipenem and meropenem), was meagre. Carbapenems are β lactam antibiotics, as are penicillins and cephalosporins, but differ from these other classes in their exact chemical structure. The bactericidal activity of carbapenem results from the inhibition of cell wall synthesis. Carbapenem penetrates the cell wall of most Gram-positive and Gram-negative bacteria to bind penicillin-binding-protein (PBP) targets.[24] ESBLs are enzymes that inactivate most penicillins, cephalosporins, and aztreonam. ESBL producing bacteria generally remain susceptible to carbapenems. Therefore, it is relevant to the current data that Carbapenem is still an effective drug for treating infections caused by ESBL producers.[25]

High resistance (>60%) to the antibiotics ciprofloxacin, levofloxacin, ampicillin, piperacillin, tetracycline, cefotaxime, cefazolin, ceftriaxone, trimethoprim-sulfamethoxazole, aztreonam, and ceftazidime was shown. This result supports another study that antimicrobial resistance among *E. coli* causing bloodstream infection was common; 36% of *E. coli* blood isolates were non-susceptible to ciprofloxacin, and 23% were non-susceptible to third-generation cephalosporins.[26] ESBLs do not inactivate non–β-lactam agents (eg, ciprofloxacin, trimethoprim-sulfamethoxazole, gentamicin). However, organisms that carry ESBL genes often carry additional genes or mutations in genes that mediate resistance to a broad range of antibiotics.

The number of ESBL-producing *E. coli* is relatively high (63%). ESBLs producing Enterobacteriaceae, including *E. coli,* can hydrolyze broad-spectrum cephalosporins, monobactams, and penicillins. Enzymes of class A β-lactamases, like TEM-1, TEM-2, and SHV-1, are responsible for the resistance to ampicillin, amoxicillin, and early generation cephalosporins. Resistance to third-generation cephalosporins arises when mutation of genes encoding TEM-1, TEM-2,

or SHV-1 gives rise to new β-lactamases that can hydrolyze them.[10]

This study's resistance rate to fluoroquinolones in ESBL-producing E. coli is high (100%). This result supports another study that extended-spectrum β-lactamase (ESBL) constitutes the most common antibiotic resistance mechanism often found on the same resistance plasmids. [27]

These epidemiological data provide good information on the resistance profile of *E. coli* causing BSI in the tertiary referral hospital. The high prevalence of bloodstream infections caused by MDRO E. coli necessitates strict infection control in order to reduce the number of MDRO *E. coli* infections in tertiary hospitals. High levels of antimicrobial resistance encourage clinicians to carry out culture and antibiotic susceptibility testing as soon as possible after the appearance of signs and symptoms of infection to provide definitive and appropriate treatment immediately. While waiting for the definitive antibiotics, the local antibiotic sensitivity pattern in the hospital needs to be taken into account to choose the right empirical antibiotics. Therefore, the role of updated epidemiology data as the guide for empirical antimicrobial therapy is essential.

CONCLUSIONS

According to epidemiology statistics, 17% of Gram-negative bacteria identified from bloodstream infections were the pathogen *E. coli*. Quinolones, ampicillin, piperacillin, tetracycline, beta-lactam antibiotics, and trimethoprim-sulfamethoxazole were all linked to high levels of antimicrobial resistance. Strict infection control is required due to the high occurrence of bloodstream infections caused by MDRO *E. coli*.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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